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(54) Title: SUSTAINED RELEASE FORMULATION

(57) Abstract

An implant formulation for the sustained release of a biologically active agent, including an effective amount of abamectin dissolved in or mixed with a carrier such as PEG 20000 which is solid or semi-solid at normal room temperature and pressure, but which melts at temperatures between 35 °C and 100 °C. An implant for delivering said formulation into a human or animal body and a method of making said implant and in addition a method for providing for the sustained release of an active agent into a human or animal body.

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SUSTAINED RELEASE FORMULATION

FIELD OF THE INVENTION

This invention relates to formulations for delivering biologically active agents to a human or an animal, and in particular it relates to sustained release formulations which may be implanted into a human or an animal for the prolonged delivery of a biologically active agent.

BACKGROUND

For many biologically active agents a preferred form of dosage is by means of the sustained release of the agent into the animal to be treated. A variety of polymeric implants are useful as delivery systems, but there is an ongoing need for improved delivery systems to be available for the treatment of both humans and animals.

It is particularly important in the treatment of livestock that biologically active agents can be administered for a prolonged period by way of a single dose, thereby avoiding the mustering of stock at regular intervals.

In particular the avermectins and milbemycins are anthelmintic groups of drugs with a broad spectrum of activity against many parasites found in livestock. At present they are usually administered as either a sub-cutaneous injection, an oral drench, or a pour-on. These forms of administration are not designed to deliver the anthelmintic agent over a prolonged period of time, and consequently blood levels of the anthelmintic are not sustained. This results in a limited period of anthelmintic activity and the need to dose the animals frequently to obtain ongoing and complete protection. Frequent dosing of livestock is onerous under pastoral conditions. Consequently, a formulation which, with one dose, could sustain the blood levels of the anthelmintic over a prolonged period would be of great value. One difficulty is that avermectins and milbemycins are very insoluble, and generally dissolve too slowly when administered under the skin to b useful. If they are first dissolved in an oil the rate of rel ase can be

More preferably the active is present in the implant at a level of 50% w/w or greater and the carrier is present at a level of 20% w/w or greater.

More preferably the implant is designed to be inserted subcutaneously.

In a further aspect the invention provides a method of providing for the sustained release of a biologically active agent into a human or animal body, which includes placing a solid or semi-solid implant into said body, said implant including an effective amount of at least one biologically active agent dissolved in and/or mixed with a carrier, said carrier being a substance which is solid or semi-solid at normal room temperature and pressure, but which melts in the range 35 to 100°C.

By wet granulation is meant the process whereby the active agent, in powder form, is mixed thoroughly with the carrier polymer, which has previously been dissolved in water. Wet granules are formed, which are then dried. The granules may then be blended with the usual excipients used in the formation of tablets. Magnesium stearate and Aerosil 200, are known in this regard. Other additives may also be added at this point. This mixture can then be compressed into tablets or implants having the desired weight and size by using well-known techniques.

By melt granulation is meant a process essentially similar to wet granulation, but in this case the active agent, in powder form, is optionally warmed, and then mixed with the carrier polymer which has been warmed and melted.

It has been found that the most suitable carriers are solid or semi-solid at 35°C and melt below 100°C. If the temperature at which the carrier melts becomes too high then there is a danger that, in the formation of the implant, the biological activity of the active ingredient will be destroyed.

While a variety of polymers are suitable for the formulation of the invention, both polyvinyl pyrrolidone, (PVP), or polyethylene glycol, (PEG) are known to be suitable, especially when the biologically active agent is an anthelmintic, and in particular, abamectin. A number of PEG polymers of the general formula $H(OCH_2CH_2)_nOH$ exist,

and the most suitable for this invention are those with an average molecular weight greater than about 1000, in particular PEG 1500, PEG 2000, PEG 4000, PEG 6000 and PEG 20000.

It has been found that by carefully controlling the ratio of the polymer to the biologically active agent the rate of release of the active can be controlled. In particular it has been found that by reducing the percentage of a carrier such as PEG to below about 40% w/w but preferably below 20% w/w and increasing the percentage of the active agent, such as abamectin, to above about 60% w/w and preferably to about 80% w/w, an initially large amount of the active agent is released for the first 10 to 20 days, followed by a lower amount being steadily released over a prolonged period of time.

It is thought that when the implant is formed, some, but not all, of the active agent dissolves in the carrier polymer. The active agent which is dissolved is released relatively quickly, as the polymer enhances the availability of it to the human or the animal body. When all the polymer has gone, the remaining active agent, which was not dissolved, continues to be released more slowly on the basis of its physical and chemical properties. If the active agent belongs to the group of the avermectins or milbemycins, the insoluble nature of the compound becomes an advantage as the release of the active agent is relatively slow as a consequence.

The rate of release of the active dissolved in the carrier can be varied by selecting a carrier with a higher or lower melting point, for example PEG 20000 instead of PEG 1500.

It is envisaged that the rate of release of the active, not dissolved in the carrier, can be enhanced, if necessary. The dissolution rate of any active can be engineered or manipulated by various well-known techniques, making it possible to optimise the release rate of the active agent by applying those techniques in conjunction with the known physical properties of the active agent. Micronisation of the active powder, inclusion of a surfactant, and the use of a disintegrating agent are three such techniques. In particular, it appears that the highly insoluble nature of abamectin is

advantageous in this context, in that it assists in the slower, subsequent release of this active, and it allows for optimisation of the rate of its release in conjunction with the techniques available, especially micronisation and the use of a disintegrating agent or surfactant.

It is particularly desirable that the carrier is biodegradable. If this is the case then once all the biologically active agent has been released there should be no residue left within the body of the animal or human, allowing for the successive use of implants without any long term detrimental effects.

The most suitable biologically active agents are those with a high activity and low required dose rate. Examples of biologically active agents which could be used, either singly or in combination, are: anthelmintics, anti-inflammatories, anti-bacterials, anti-parasitic agents, anti-virals, anti-fungals, analgesic agents, vaccines and others.

PREFERRED EMBODIMENTS

The above and other aspects of the invention which should be considered in all its novel aspects will be apparent from the following examples.

Example 1.

An implant having a total weight of 250mg, and a diameter of 5mm, and a thickness of about 3mm, was prepared from 50mg of abamectin and 200mg PEG 2000, (20% w/w abamectin, 80% w/w PEG 2000). The implant was prepared by melt granulation and granulation. The implant is suitable for subcutaneous insertion in the ear of an animal.

Example 2.

An implant as described in Example 1, but containing 125mg of abamectin and 125mg PEG 2000, (50% w/w abamectin and 50% w/w PEG 2000).

Example 3.

An implant as described in Example 1, but containing 167.5mg of abamectin and 82.5mg PEG 20000, (67% w/w abamectin and 33% w/w PEG 20000).

Example 4.

An implant as described in Example 1, but containing 200mg of abamectin and 50mg PEG 20000, (80% w/w abamectin and 20% w/w PEG 20000).

Example 5.

An implant as described in Example 4 containing 200mg of abamectin and 50mg PEG 20000, (80% w/w abamectin and 20% w/w PEG 20000), but which has been prepared by means of wet granulation and compression.

Example 6.

An implant as described in Example 3 containing 167.5mg of abamectin and 82.5mg PEG 20000, (67% w/w abamectin and 33% w/w PEG 20000), but which has been prepared by means of wet granulation and compression.

Example 7

An implant having a total weight of 250mg, and a diameter of 5mm, and a thickness of about 3mm, was prepared from 50mg of ivermectin and 200mg PEG 20000, (20% w/w ivermectin, 80% w/w PEG 20000). The implant was prepared by melt granulation and granulation. The implant is suitable for subcutaneous insertion in the ear of an animal.

Example 8.

An implant as described in Example 7, but containing 125mg of ivermectin and 125mg PEG 20000, (50% w/w ivermectin and 50% w/w PEG 20000).

Example 9.

An implant as described in Example 7, but containing 167.5mg of ivermectin and 82.5mg PEG 20000, (67% w/w ivermectin and 33% w/w PEG 20000).

TRIAL DATA

1. Selection of Polymer

Initial trials were conducted to select the most suitable polymers for the in vivo animal studies to be conducted. These trials lead to the selection of PEG (polyethylene glycol) and PVP (polyvinyl pyrrolidone) as the most promising polymers to be used. The trials investigated the release of abamectin from a series of formulations with different percentages of carrier to abamectin. The first set focussed on PVP as the carrier, the second used PEG. For the purposes of this study PEG 20000 was used.

The results are displayed in Figures 1 and 2 respectively.

Figure 1: Abamectin release as a function of time at different PVP concentrations.

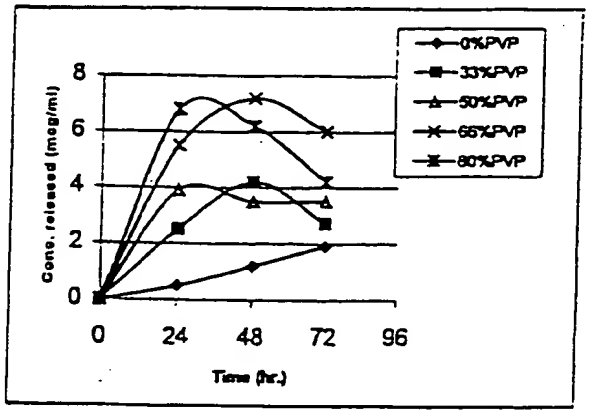
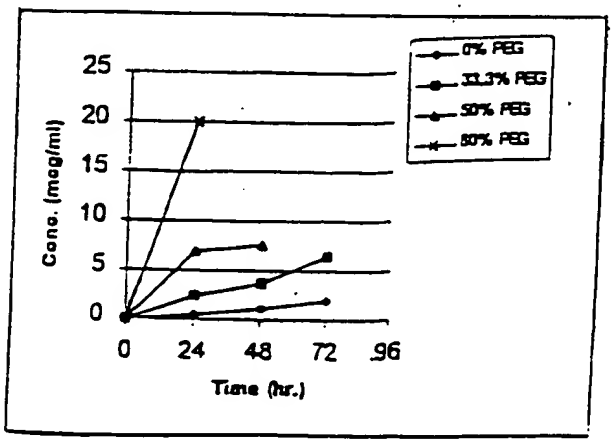


Figure 2: Abamectin release as a function of time at different PEG concentrations.



Based on these results it was decided to use only PEG 20000 for the in vivo study.

2. In Vivo Testing of Implants - First study

Three formulations, A, B, and C were initially selected and prepared for study. Implants weighing 250mg and about 5mm in diameter were prepared from the formulations, and implanted into the base of the ear of a sheep. The compositions of A, B and C were:

A - 20% w/w abamectin and 80% w/w PEG 20000

B - 50% w/w abamectin and 50% w/w PEG 20000

C - 67% w/w abamectin and 33% w/w PEG 20000

All the formulations were prepared by melt granulation.

The following TABLE 1 and associated graph, give the concentration of active in the plasma, in ng/mL over days 3 to 70.

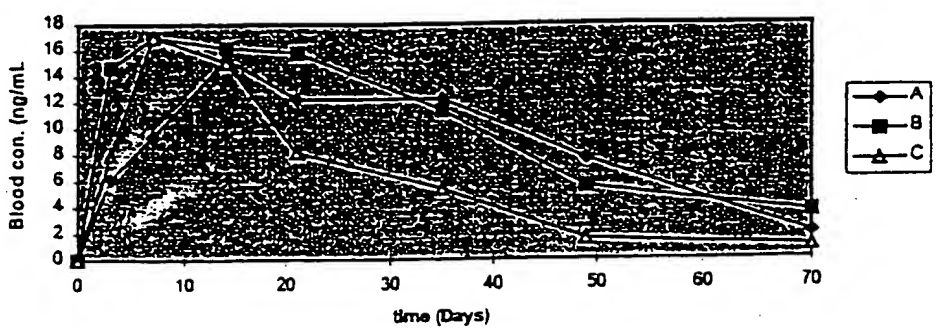
Table 1: Concentration of abamectin in plasma (ng/mL)

	Day	3	7	14	21	35	49	70
Formula	Sheep							
A	1	10	19.4	14.7	6.7	15.4	5.6	1.6
	2	5.2	4.1	11.9	10.2	10.9	6.5	1.6
	3	3.5	4.7	19.4	20	10.9	11.1	2.99
	Mean ± SD	6.2±3.4	9.4±8.7	15.3±3.8	12.3±6.9	12.4±2.6	7.7±3.0	2.0±0.8
B	1	20.5	19.4	14.0	18.0	8.6	5.6	1.6
	2	19.4	17.6	18.8	12.7	10.9	5.6	4.0
	3	1.4	14.1	16.0	16.7	14.7	5.6	5.2
	Mean ± SD	14.7±9.2	17.0±2.7	16.2±2.4	15.8±2.8	11.4±3.1	5.6±0	3.6±1.8
C	1	5.2	24.7	31.8	12.7	7.9	4.7	2.9
	2	10.5	17.6	9.9	6.0	5.6	0	0
	3	8.2	8.8	3 7	6.0	2.6	1.1	0
	Mean ± SD	8.0±2 7	17.0±8 0	15 1±4 8	8.2±3.9	5.4±3 9	1 9±2 5	1 0±1 7

Table 2: Pharmakokinetic Parameters of Abamectin Implants

Parameters	Formulation A	Formulation B	Formulation C
Cmax (ng/mL)	17.0±4.4	18.8±2.1	19.4±11.6
Tmax (days)	14±7	9±10	9±4
AUC ng mL^{-1} day	641.5±122.9	721.2±19.2	415.2±237.9

Figure 3: Time Course for Abamectin Implant



3. *In vivo* Testing of Implants - Second Study

Group 1: two implants, 33mg abamectin and 20% PEG 20000.

Group 2: three implants, 50mg abamectin and 20% PEG 20000.

Group 3: two implants 33mg abamectin and 20% PEG 20000.

Group 4: three implants 50mg abamectin and 20% PEG 20000.

Group 1 and 2 used small abamectin particles whereas those used in Groups 3 and 4 were large.

Table 3: The plasma abamectin concentration (ng/mL) versus time data for each sheep.

	Day Sheep	0	2	4	8	15	21	35	49	87
Group 1*	1	0.0	2.6	2.2	28.6	19.5	12.4	2.0	0.4	6.8
	2	0.0	0.6	1.1	11.4	10.5	15.8	4.8	6.0	0.0
	3	0.0	2.6	1.9	8.0	28.5	13.5	3.1	4.1	0.0
	4	0.0	0.9	0.8	10.0	14.1	26.8	24.0	8.8	0.0
Group 2	1	0.0	6.0	2.8	7.6	31.2	24.6	13.3	10.5	0.0
	2	0.0	7.1	19.5	45.4	21.6	17.8	5.7	7.8	0.0
	3	0.0	4.0	4.0	30.4	23.9	14.4	6.8	4.8	7.1
	4	0.0	2.74	5.4	12.9	18.3	21.5	5.1	7.1	0.0
Group 3	1	0.0	4.3	10.6	23.3	33.4	21.5	11.3	7.5	2.2
	2	0.0	3.7	0.9	15.2	17.7	14.4	5.9	2.5	0.0
	3	0.0	0.8	1.2	11.2	35.0	11.3	7.4	6.0	8.6
	4	0.0	1.2	0.8	0.0	33.7	38.3	13.3	6.7	6.1
Group 4	1	0.0	2.0	1.2	6.0	17.5	18.9	9.8	4.6	0.0
	2	0.0	1.2	2.3	10.2	24.9	26.6	25.3	12.9	5.6
	3	0.0	1.6	2.5	7.9	24.7	15.5	9.8	9.2	0.0
	4	0.0	3.7	4.0	5.6	21.6	26.4	7.7	4.6	0.0

* Value of abamectin concentration are mean, n=2

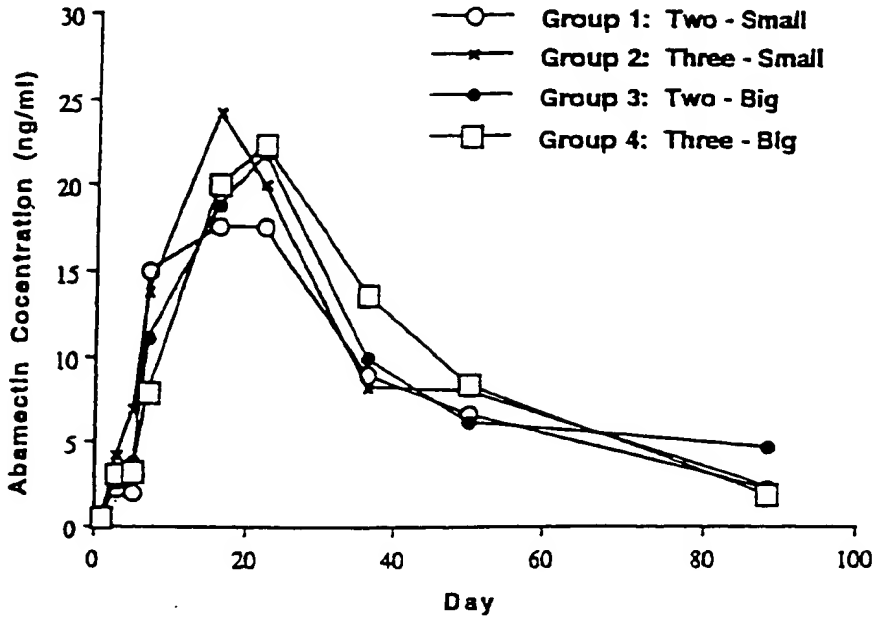
Table 4: Pharmacokinetics Parameters of Abamectin Implant

Parameters	Group 1	Group 2	Group 3	Group 4
Cmax (ng/mL)	24.9±6.1	26.2±5.4	22.8±10.9	22.6±4.5
Tmax (day)	15.7±7.1	14.3±6.2	18.0±3.5	19.5±3.0
AUC	636.2±249.1	168.5±187.2	726.1±172.3	895.6±381.7

Table 5: Egg counts

Groups	Sheep Code No	Day 0	Day 2	Day 4	Day 8	Day 15	Day 21	Day 35	Day 49	Day 87
1.1	167	5	0	0	0	5	15	15	90	15
1.2	155	35	10	15	0	15	25	5	5	10
1.3	150	105	10	10	0	155	55	10	0	10
1.4	166	5	0	70	5	5	10	10	5	45
	Mean	37.5	5	23.75	1.25	45	26.25	10	25	20
	S.D.	47.2	5.8	31.5	2.5	73 5	20 2	4.1	43.4	16.8
	% Variation	125.8	115 5	132 5	200.0	163 3	76 8	40.8	173.6	84.2
2.1	163	60	5	0	5	5	45	10	100	5
2.2	164	0	0	0	5	0	0	0	0	15
2.3	160	5	0	0	0	0	0	0	25	0
2.4	165	0	50	0	0	10	5	5	0	5
	Mean	16.25	13.75	0	2.5	3.75	12.5	3.75	31.25	6.25
	S.D.	29.3	24.3	0.0	2.9	4.8	21.8	4.8	47.3	6.3
	% Variation	180.1	176.6	0.0	115.5	127 7	174.4	127.7	151.4	100 7
3.1	156	100	10	0	10	5	0	0	0	30
3.2	162	0	5	5	0	10	5	5	0	55
3.3	161	10	0	0	0	25	0	0	0	5
3.4	154	25	15	0	5	10	5	5	20	20
	Mean	33.75	7.5	1.25	3.75	12.5	2.5	2.5	5	27.5
	S.D.	45.3	6 5	2 5	4.8	8.7	2.9	2.9	10.0	21.0
	% Variation	134 4	86 1	200 0	127 7	69.3	115.5	115.5	200.0	76 4
4.1	152	10	5	0	5	185	0	0	0	30
4.2	158	20	10	55	0	10	0	0	10	15
4.3	157	10	5	20	5	5	5	5	0	25
4.4	151	20	0	10	0	60	15	15	25	35
	Mean	15	5	31.25	2.5	65	5	5	8.75	36.25
	S.D	5 8	4 1	23 9	2 9	83 8	7 1	7.1	11.8	8.5
	% Variation	38 5	81.6	112 6	115.5	128 9	141 4	141.4	135.0	32.5
Control 1	153	130	235	80	75	475	125	100	125	135
Control 2	159	65	145	105	65	305	155	160	75	155
	Mean	59.8	116.4	80.4	64.6	248.2	107.1	102.1	86.7	82.8
	S.D.	52 7	97 3	40 1	46 6	178 8	67 8	68.2	56 4	73 0
	% Variation	88 :	84 0	49 9	72 1	72 1	63 3	66 7	65 :	88 2

Fig 4: The mean plasma concentration of abamectin (n=4) after the dosing abamectin implant from the four formulations studied.



ADVANTAGES OF PREFERRED EMBODIMENTS

In the sustained delivery of biologically active agents, and in particular anthelmintics, it is often desirable to have a large amount of the active agent released initially, followed by a smaller amount released steadily over a prolonged period of time. In the past it has only been possible to achieve two different rates of release of an active agent by means of two tablets sandwiched together. In certain of the preferred embodiments of this invention it is now possible to achieve this dual rate of release from a single dosage, by way of the implant of this invention.

In particular it has been discovered that biologically active agents such as avermectins or milbemycins, can be formulated into a single sustained release formulation in which the active is able to be released slowly over a prolonged period of time, but which may also deliver an initial boost of the biologically active agent in the immediate period after dosing.

VARIATIONS

In addition to changing the ratio of the active to carrier, the rate of release of the active can also be manipulated by changing the carrier to one with a higher or lower melting point. This will affect the rate of dissolution of the carrier and consequently the rate of release of the dissolved active.

The active in the formulation may be micronised or alternately a disintegrating agent may be included in the formulation. This would help prolong the activity of the non dissolved active. Alternately the release in the second phase may be prolonged by delaying the release of PEG by using a higher molecular weight PEG, complexing the PEG or using a coat which is released after 40 to 50 days.

Alternatives to PEG may be useful in prolonging this second phase.

Finally it will be appreciated that various other alterations and modifications may be made to the foregoing without departing from the scope of the invention.

WHAT WE CLAIM IS:

1. A formulation for the sustained release of a biologically active agent, including an effective amount ~~of~~ at least one biologically active agent dissolved in an/or mixed with a carrier, said carrier being a substance which is solid or semi-solid at normal room temperature and pressure, but which melts in the range of 35 to 100°C.

2. A formulation as claimed in claim 1 wherein, the biologically active agent is an anthelmintic.

3. A formulation as claimed in any prior claim wherein the carrier is a polymer having a molecular weight greater than 1000.

4. A formulation as claimed in any prior claim wherein the carrier is present in the range from 20% w/w to 80% w/w.

5. A formulation as claimed in any prior claim wherein the active agent is present in the range from 20% w/w to 80% w/w.

6. A solid or semi-solid implant for the sustained release of the biologically active agent, said implant including an effective amount of at least one biologically active agent dissolved in and/or mixed with a carrier, said carrier being a substance which is solid or semi-solid at normal room temperature and pressure, but which melts in the range 35 to 100°C.

7. An implant as claimed in claim 6 wherein, the solid or semi-solid implant is adapted to provide an initially high rate of release of the biologically active agent for a short time, followed by a slower rate of release at a prolonged period of time.

8. An implant as claimed in claim 7 wherein the active is present at a level of 50% w/w or greater and the carrier is present at a level of 20% w/w or greater.

9. An implant as claimed in claims 6, 7, or 8 wherein the implant is designed to be inserted subcutaneously.

10. A method of providing for the sustained release of a biologically ~~active~~ agent into a human or animal body, which includes placing a solid or semi-solid implant into said body, said implant including an effective amount of at least one biologically active agent dissolved in and/or mixed with a carrier, said carrier being a substance which is solid or semi-solid at normal room temperature and pressure, but which melts in the range 35 to 100°C.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ 99/00037

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]. A61K 009/00; A61K 047/30; A61K 047/32; A61K 047/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K, Search Terms as below

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT WPAT CA (STN): (PEG or polyethylene () glycol or PVP or polyvinyl () pyrrolidone) AND (anthelmintic or abamectin or milbemycin or avermectin or ivermectin)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Gennaro, A.R. (Ed.) "Remington's Pharmaceutical Sciences, 17th Ed." (Mack Publishing Co., Pennsylvania, U.S.A., 1985) see pages 1656-1658	1,6,10
X	Johnson, J.C. (Ed.) "Sustained Release Medications" (Noyes Data Corporation, New Jersey, USA. 1980) see pages 172-177, 374-377	1, 3-6, 8-10
X	AU-B-71725/96 (679150) (LG Chemical Ltd.) 19 June 1997 see whole document	1, 3-10

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 1999	14 JUL 1999
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No : (02) 6285 3929	Authorized officer MICHAEL GRIEVE Telephone No.: (02) 6283 2267

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ 99/00037

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU-A-52718/93 (Lucky Limited) 7 July 1994 see whole document	1, 3-6, 9-10
X	US 4053580 (G.D Searle & Co.) 11 October 1977 see whole document	1, 3-6, 9-10
X	AU-A-60614/85 (Alza Corporation) 12 February 1987 see whiole document, especially page 9 lines 1 to 15, and page 27 lines 14-27	1-6, 8-10
X	GB 2154138 A (Drug Systems Research and Development Limited) 4 September 1985 see whole document, especially page 1 lines 44 to 45	1-6, 8-10
P,X	WO 99/15166 (Pfizer Limited) 1 April 1999 see whole document	1-6, 8-10
X	US 5403593 (Sandoz Ltd.) 4 April 1995 see whole document, especially column 8 lines 3 to 28	1-6, 8-10
X	WO 97/49384 (Board of Regents, The University of Texas System) 31 December 1997 see whole document, especially page 9 line 25	1-6, 8-10
X	AU-A-75739/81 (Minnesota Mining and Manufacturing Co.) 8 April 1982 see whole document	1-5
X	US 4595583 (Alza Corporation) 17 June 1986 see whole document, especially column 12 lines 30-45	1-5
X	AU-A-60880/86 (Alza Corporation) 19 February 1987 see whole document, especially page 22	1-5
X	US 4927633 (Alza Corporation) 22 May 1990 see whole document, especially column 19 lines 23 to 39	1-5
X	AU-A-27505/88 (Ancare Distributors Limited) 20 July 1989 see whole document	1-5
P,X	AU-A-59367/98 (Biogenesis Sociedad Anonima) 24 September 1998 see whole document	1-5

AUSTRALIAN PATENT OFFICE
SEARCH REPORT

Application No.
NZ 99/00037

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 173293 A (Merrell Dow Pharmaceuticals Inc.) 5 March 1986 —— See whole document	1, 3-5
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/NZ 99/00037

This Annex lists the krfown "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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		US	5662917				
US	4053580	AR	206946	AT	8127/75	AU	85974/75
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		DK	4782/75	ES	442017	FR	2289207
		GB	1522846	JP	51067719	NL	7512430
		US	3946106	ZA	7506352	US	3992518
AU	60614/85	US	4692336	BE	905214	BR	8603651
		CA	1244738	DE	3625854	ES	556147
		ES	8802112	FR	2585949	GB	2178656
		IT	1195817	JP	62034576	NL	8601960
		NZ	216966	ZA	8605827	AU	39242/85
		BE	901941	CA	1221587	DE	3509410
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		US	4717568	US	4717718	US	4729793
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		US	5000957	AR	240399	AU	60697/86
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		CA	1278968	DE	3625915	ES	556303

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		IT	1195818	JP	62039518	NL	8601971
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WO	49384/97	AU	35080/97				
AU	75739/81	AR	229104	CA	1138333	EP	49068
		NZ	198494	US	4326524		
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		JP	62044247	NL	8601993	NZ	217053
		US	4704118	ZA	860613	US	4871544
		US	4883667	US	4955881	US	4966767
		US	5098425				
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		ES	546545	ES	8608866	FI	853275
		GR	852078	HU	38248	IL	76237
		JP	61060613	NZ	213248	PH	21083
		PT	81028	ZA	8506482	CN	85106652
AU	70956/87	CA	1314480	DE	3610878	DK	1628/87
		EP	239983	FI	871378	IL	82065
		JP	63008327	NO	871350	NZ	219823
		PT	84604	ZA	8702326		
							END OF ANNEX